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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,979	07/11/2003	Tina M. Henkin	22727/04130	8217

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/617,979	HENKIN ET AL.	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-17 and 35* is/are withdrawn from consideration.

5)☒ Claim(s) *30-34* is/are allowed.

6)☒ Claim(s) *18-28* is/are rejected.

7)☒ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____. 10/17/03, 10/31/03, 7/29/04, 8/4/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 18-34, in the reply filed on 8/28/2006 is acknowledged. Claims 1-17 and 35 are withdrawn from further consideration.

Information Disclosure Statement

Certain references on the information disclosure statements of 10/17/2003, 10/31/2003 and 6/29/2004 have been lined through only because they are duplicated on another IDS. These references have been considered, however.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-21, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grundy et al (2002, cited reference AT on the IDS of 10/17/2003) in view of Di Nocera et al (1975) and Kirschbaum et al (USPN 6,174,722 B1).

With regard to claim 18, Grundy (2002) teaches a reaction mixture (in vitro transcription reaction) that comprises:

a template DNA that comprises (i) a bacterial promoter (*tyrS* promoter; page 1648, column 2, "*In vitro* transcription assays")

(ii) a leader of a T-box regulated gene, including a transcription start site,(*tyrS* leader; page 1648, column 2, "*In vitro* transcription assays" and figure 3) *and*

(iii) a downstream polynucleotide of sufficient length for detection of a read-through mRNA product (see products of transcription shown in figure 3); *divalent metal cations* (Mg^{2+}; page 1648, column 2, "*In vitro* transcription assays"

and figure 3); *nucleoside triphosphates* (page 1648, column 2, "*In vitro* transcription assays" and figure 3); *bacterial RNA polymerase complex* (*B. subtilis* RNAP; page 1648, column 2, "*In vitro* transcription assays" and figure 3); *and tRNA specific for a specifier sequence located in the leader* ($tRNA^{Tyr}$; page 1648, column 2, "*In vitro* transcription assays" and figure 3). Grundy (2002) also teaches the addition of NusA protein to some reaction mixtures (page 1648, column 2, "*In vitro* transcription assays" and figure 3). NusA is a *potential inhibitor substance*.

Grundy (2002) does not teach *dinucleotides corresponding to and encoded by the transcription start site of the leader*.

Di Nocera teaches that "[t]he use of dinucleotides in *in vitro* transcription systems can, therefore, also be a useful tool in studying regulation of gene expression *in vitro*" (page 8380, penultimate sentence of penultimate paragraph of column 1). Di Nocera teaches all dinucleotide combinations of A, C, G and U (see table 1), which would necessarily include *dinucleotides corresponding to and encoded by the transcription start site of the leader*.

Di Nocera does not teach T-box regulated genes in an *in vitro* transcription assay or screening potential inhibitor substances.

The concept of using *in vitro* transcription processes for screening natural products and other chemical substances was known in the art, as shown by Kirschbaum (USPN 6,174,722 B1, entitled "*In vitro* Transcription Processes For Screening Natural Products And Other Chemical Substances"). Kirschbaum specifically teaches carrying out transcription processes in the presence and

absence of an active substance to be tested, and determining the activity (e.g. inhibitory or activating) from the difference in the amount of transcripts produced (column 14, lines 15-28).

It would have been *prima facie* obvious to one of ordinary skill in the art to include dinucleotides in the *in vitro* transcription reactions taught by Grundy (2002). One would have been motivated to do this because Di Nocera taught that this was useful, as discussed above. One would also have been motivated to use the *in vitro* transcription system taught by Grundy (2002) to screen for inhibitors, since the use of *in vitro* transcription to screen for inhibitory substances was known, as shown by Kirschbaum.

With regard to claim 19, Grundy (2002) teaches Mg^{2+} (page 1648, column 2, "*In vitro* transcription assays" and figure 3).

With regard to claim 20, Grundy (2002) teaches ATP, CTP, GTP and UTP (page 1648, column 2, "*In vitro* transcription assays" and figure 3).

With regard to claim 21, Di Nocera teaches all dinucleotides listed (see table 1).

With regard to claim 23, Grundy (2002) teaches that the template for the in vitro transcription analysis comprised the *tyrS* promoter, leader and leader region terminator followed by the tandem terminators from the *B. subtilis tyrS* and *rpsD* genes, referring to Henkin et al, 1992 (page 1648, column 2, "*In vitro* transcription assays" and figure 3). As evidenced by figure 2 of Henkin et al, 1992, the transcriptional terminator of the *B. subtilis tyrS* gene (inverted arrows in

figure 2) is seen to comprise between about 30 to about 150 nucleotides in length:

FIG. 2. Nucleotide sequence of the *tyrS* gene. The DNA sequence of 1.8 kb of the 2.0-kb *Hin*dIII fragment is shown; the end of this sequence overlaps the *rpsD* sequence previously reported (15). The predicted TyrTS amino acid sequence is shown above the DNA sequence. Restriction sites are labeled below the DNA sequence. The promoter sequence (−35, −10, +1), ribosome-binding site (S.D., ATG), and T-box sequence are underlined. The putative transcriptional terminators are shown as inverted dashed arrows.

Therefore the template in the *in vitro* transcription reaction taught by Grundy (2002) necessarily meets the limitation *wherein the downstream polynucleotide of sufficient length for detection of a read-through mRNA product comprises a polynucleotide which is from about 30 to 150 nucleotide residues in length.*

With regard to claim 25, Grundy (2002) teaches *B. subtilis* RNAP; page 1648, column 2, "*In vitro* transcription assays" and figure 3.

Claims 22 and 24 rejected under 35 U.S.C. 103(a) as being unpatentable over Grundy et al (2002, cited reference AT on the IDS of 10/17/2003) in view of Di Nocera et al (1975) and Kirschbaum et al (USPN 6,174,722 B1) as applied to claims 18-21, 23 and 25 above, and further in view of Chopin et al (1998).

With regard to claims 22 and 24, the combined teachings of Grundy (2002), Di Nocera and Kirschbaum meet the limitations of claim 18, upon which claims 22 and 24 depend, as discussed above. These references do not teach the *B. subtilis glyQS* or *B. subtilis rpsD* promoters or $tRNA^{Gly}$.

Chopin teaches that the *B. subtilis glyQS* is also a T-box regulated gene (see for example table 1, page 663). Chopin does not teach *a template DNA that comprises (i) a bacterial promoter, (ii) a leader of a T-box regulated gene,*

including a transcription start site, and (iii) a downstream polynucleotide of sufficient length for detection of a read-through mRNA product; divalent metal cations; nucleoside triphosphates; dinucleotides corresponding to and encoded by the transcription start site of the leader; bacterial RNA polymerase complex; and tRNA specific for a specifier sequence located in the leader. Chopin also does not teach a *potential inhibitor substance.*

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to substitute the *B. subtilis glyQS/tRNA*^{Gly} system taught by Chopin for the *tyrS/tRNA*^{Tyr} system taught by Grundy (2002), Di Nocera and Kirschbaum since both systems were known in the prior art as T-box regulated systems. Regarding the obviousness of substituting equivalents known for the same purpose, MPEP 2144.06 states: "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." In this case, Chopin clearly establishes that the *B. subtilis glyQS/tRNA*^{Gly} system was an art recognized equivalent of the *tyrS/tRNA*^{Tyr} system taught by Grundy (2002).

Claim 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grundy et al (2002, cited reference AT on the IDS of 10/17/2003), Di Nocera et al (1975) and Kirschbaum et al (USPN 6,174,722 B1) as applied to claims 18-

21, 23 and 25 above, and further in view of Chopin et al (1998) and Grundy et al (1997).

With regard to claims 26-28, the combined teachings of Grundy (2002), Di Nocera and Kirschbaum meet the limitations of claim 18, upon which claims 26-28 depend, as discussed above. These references do not teach the *B. subtilis glyQS* or *B. subtilis rpsD* promoters or *tRNA*^{Gly} (claims 26 and 28). These references also do not teach modifying the specifier or terminator sequences of the leader (claims 26 and 28), modifying the anticodon or discriminator sequence of the tRNA or the transcription start site of the leader (claims 27 and 28).

Grundy (1997) teaches modifying the specifier sequence of the leader of a T-box regulated gene (*tyrS*; see page 2587, last paragraph of column 1, and page 2588, column 2, "Specifier sequence switches in the *B. subtilis tyrS* leader"). Grundy (1997) also teaches modifying the anticodon of a tRNA (see page 2591, 1st paragraph of section entitled "Mutants of tRNA^{Thr} with improved induction of *tyrS*", continuing on page 2592).

Grundy (1997) teaches making these modifications in a genetic (i.e. cell-based) assay, which cells necessarily comprise *a template DNA that comprises (i) a bacterial promoter, (ii) a leader of a T-box regulated gene, including a transcription start site, and (iii) a downstream polynucleotide of sufficient length for detection of a read-through mRNA product; divalent metal cations; nucleoside triphosphates; bacterial RNA polymerase complex; and tRNA specific for a specifier sequence located in the leader.*

Grundy (1997) does not teach *dinucleotides corresponding to and encoded by the transcription start site of the leader* or a *potential inhibitor substance*.

Chopin teaches that the *B. subtilis glyQS* is also a T-box regulated gene (see for example table 1, page 663). Chopin does not teach *a template DNA that comprises (i) a bacterial promoter, (ii) a leader of a T-box regulated gene, including a transcription start site, and (iii) a downstream polynucleotide of sufficient length for detection of a read-through mRNA product; divalent metal cations; nucleoside triphosphates; dinucleotides corresponding to and encoded by the transcription start site of the leader; bacterial RNA polymerase complex; and tRNA specific for a specifier sequence located in the leader.* Chopin also does not teach a *potential inhibitor substance.*

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to substitute the *B. subtilis glyQS/tRNA*^{Gly} system taught by Chopin for the *tyrS/tRNA*^{Tyr} system taught by Grundy (2002), Di Nocera and Kirschbaum since both systems were known in the prior art as T-box regulated systems. Regarding the obviousness of substituting equivalents known for the same purpose, MPEP 2144.06 states: "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." In this case, Chopin clearly establishes

that the *B. subtilis glyQS/tRNA*^{Gly} system was an art recognized equivalent of the *tyrS/tRNA*^{Tyr} system taught by Grundy (2002).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the specifier sequence of the leader and the anticodon of the tRNA in order to obtain "improved induction", as taught by Grundy (1997).

In *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties"

Here, the prior art structures of the leaders of *B. subtilis tyrS* (Grundy, 1997, figure 1) and *B. subtilis glyQS* (Chopin, table 1) were known. Therefore, as stated by the court, one of ordinary skill in the art would have contemplated making homologs "to try to obtain compounds with improved properties". The obviousness to modify the leader or tRNA sequences is further evidenced by Grundy (1997), who in fact performed these modifications with success in the case of the *B. subtilis tyrS* example (page 2587, last paragraph of column 1; page 2588, column 2, "Specifier sequence switches in the *B. subtilis tyrS* leader"; page 2591, 1st paragraph of section entitled "Mutants of tRNA^{Thr} with improved induction of *tyrS*", continuing on page 2592).

Allowable Subject Matter

Claim 29 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 30-34 are allowed.

While the prior art teaches an *in vitro* transcription assay for a T-box regulated gene (Grundy, 2002) and provides motivation to include dinucleotides (Di Nocera) and use such assays to screen for inhibitors (Kirschbaum), there is no teaching or suggestion in the prior art to modify the *in vitro* transcription assay reaction mixture taught by Grundy (2002) to include a halted complex.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

scw

JEFFREY FREDMAN
PRIMARY EXAMINER